REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

The Restriction Requirement indicates that Groups 1-14 are drawn to a nucleic acid encoding a protein of amino acid sequence as set forth in SEQ ID NO:1-8 and SEQ ID NO:10-15 (Office Action, May 16, 2003; page 2 at § 2). Applicants respectfully point out that the claims are also drawn to polynucleotides comprising the polynucleotide sequence of SEQ ID NO:24. For example, claim 10, as amended, recites isolated polynucleotides "comprising a polynucleotide sequence selected from the group consisting of **SEQ ID NO:16-30**." For at least this reason, this Restriction Requirement should be withdrawn.

In response to the Restriction Requirement, Applicants hereby elect the claims of Group 13 (including claims 3-5 and 9-14), drawn to polynucleotides encoding SEQ ID NO:14, polynucleotides comprising SEQ ID NO:29, host cells, vectors, and a method of making polypeptides encoded by the polynucleotides, with traverse. In response to the requirement for election of a sequence, Applicants provisionally elect the species of SEQ ID NO:14 (which is encoded by a polynucleotide having the sequence of SEQ ID NO:29), also with traverse. Applicants traverse both requirements on the following grounds:

I. The Unity of Invention standard **must** be applied in national stage applications

Section 1850 of the Manual of Patent Examining Procedure (February 2003 revision of the original 8th edition) (hereinafter "M.P.E.P.") provides:

> . . . [W]hen the Office considers international applications . . . during the national stage as a Designated or Elected Office under 35 U.S.C. 371, PCT Rule 13.1 and 13.2 will be followed when considering unity of invention of claims of different categories without regard to the practice in national applications filed under 35 U.S.C. 111. . .

> In applying PCT Rule 13.2 to . . . national stage applications under 35 U.S.C. 371, examiners should consider for unity of invention all the claims to different categories of invention in the application and permit retention in the same application for searching and/or preliminary examination, claims to the categories which meet the requirements of PCT Rule 13.2.

M.P.E.P. section 1893.03(d) reiterates the Patent Office's obligation to apply the Unity of Invention standard PCT Rule 13.2 instead of U.S. restriction/election of species practice:

> Examiners are reminded that unity of invention (not restriction) practice is applicable . . . in national stage applications submitted under 35 U.S.C. 371.

Specific provisions of the Administrative Regulations Under the PCT and the corresponding provisions of the M.P.E.P. strongly support a finding of unity of invention among all of the claims in the present case:

Unity of Invention is accepted as between claims to polypeptides and claims to the polynucleotides which encode them

Example 17, Part 2 of Annex B to the Administrative Regulations Under the PCT provides that unity of invention is accepted as between claims to polypeptides and claims to polynucleotides encoding those polypeptides. Those Examples are cited in M.P.E.P. section 1893.03(d) ("[n]ote also examples 1-17 of Annex B Part 2 of the PCT Administrative Instructions . . .").

Thus, in the present case, unity of invention exists at least as between claims drawn to polypeptides of SEQ ID NO:1-8 and SEQ ID NO:10-15 (e.g., claim 1) and claims drawn to polynucleotides which encode those polypeptides (e.g., claims 3-4 and 9-13).

Unity of Invention exists with respect to dependent claims in the same claim category as the independent claim from which they depend

Section A of M.P.E.P. section 1850, which recites the provisions of paragraph (c) of Part 1 (entitled "Instructions Concerning Unity of Invention") of Annex B (entitled "Unity of Invention") to the Administrative Instructions Under the PCT, provides:

A. Independent and Dependent Claims

Unity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims. By "dependent" claim is meant a claim which contains all the features of another claim and is in the same category of claim as that other claim (the expression "category of claim" referring to the classification of claims according to the subject matter of the invention claimed, for example, product, process, use or apparatus or means, etc.).

If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims. In particular, it does not matter if a dependent claim itself contains a further invention. . . (M.P.E.P. section 1850 at section A; see also M.P.E.P. Appendix AI)

In the present case, claims 4, 5, 12, and 13, all of which depend from claim 3, are directed to compositions of matter (i.e., to products). Claims 4, 5, 12, and 13 contain all of the features of claim 3. Furthermore, claim 1 is dependent on claim 3, and claim 1 contains all of the features of claim 3. Therefore, since both claims 1 and 3 are directed to compositions of matter (i.e., to products), there is unity of invention as between claim 1 and claim 3.

Thus, it is improper to restrict claim 1 from claims 3-5, 12, and 13, as the Patent Office has done. Therefore, Applicants respectfully request that the Examiner withdraw the Restriction Requirement at least as to the composition of matter claims, and that at least those claims be considered together in a single application.

Unity of Invention exists as between all of Applicants' claims

M.P.E.P. section 1850 provides:

Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more special technical features. The term "special technical feature" is defined as meaning those technical features that define a contribution which each of the inventions considered as a whole, makes over the prior art. The determination is made based on the contents of the claims as interpreted in light of the description and drawings. Annex B also contains examples concerning unity of invention.

M.P.E.P. section 1893.03(d) similarly provides:

> A group of inventions is considered linked to form a single general inventive concept where there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature. The expression special technical features is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. For example, a corresponding technical feature is exemplified by a key defined by certain claimed structural characteristics which correspond to the claimed features of a lock to be used with the claimed key. Note also examples 1-17 of Annex B Part 2 of the PCT Administrative Instructions as amended July 1, 1992 contained in Appendix AI of the MPEP.

In the present case, unity of invention exists among all of Applicants' claims. The sequences of the claimed polypeptides and the sequences of the claimed polynucleotides encoding those polypeptides are corresponding technical features which are common to all of Applicants' claims. These corresponding technical features serve to technically interrelate all of Applicants' claims, and define the contribution over the prior art made by each of them. Thus, Applicants' claims are linked to form a single general inventive concept, and Applicants are therefore entitled to prosecute all of their pending claims in a single national stage application.

<u>The sequences of the claimed polypeptides, and of the claimed polynucleotides encoding those polypeptides, are corresponding technical features that are common to all of Applicants' claims, and serve to technically interrelate them</u>

Applicants' claims recite *inter alia* the polypeptides of SEQ ID NO:1-8 and SEQ ID NO:10-15, polynucleotides encoding those polypeptides (including the polynucleotides of SEQ ID NO:16-23 and SEQ ID NO:25-30), and polynucleotides comprising SEQ ID NO:24. The sequences of the claimed polypeptides and of the corresponding polynucleotides are common to all of Applicants' claims, given that each claim refers to one or both either explicitly or implicitly (by virtue of depending from a claim which makes explicit reference to the sequences of the claimed polypeptides or the claimed polynucleotides).

Moreover, the sequences of the claimed polypeptides and of the corresponding polynucleotides serve to technically interrelate all of Applicants' claims. Applicants' composition of matter claims (e.g.,

claims 1, 3-5, 9-13, and 16) are drawn to either the polypeptides or polynucleotides themselves (e.g., claim 1, drawn to polypeptides; and claims 3-5 and 9-11, drawn to polynucleotides), to compositions of matter which comprise the polypeptides or polynucleotides as one element (e.g., claim 12, drawn to recombinant polynucleotides; and claim 13, drawn to transformed cells), or to compositions of matter wherein the sequences of the claimed polypeptides functionally limit the claimed subject matter (e.g., claim 16, drawn to an antibody which specifically binds to a polypeptide of claim 1).

In Applicants' method claims (e.g., claims 7, 8, and 14), the claimed polypeptides or polynucleotides serve as either the product of the claimed method (e.g., claim 14, drawn to methods of producing the claimed polypeptides) and/or as a reagent for performing the method (e.g., claim 14, drawn to methods of using the claimed polynucleotides to produce polypeptides; and claims 7 and 8, drawn to methods of detecting the claimed polynucleotides).

Therefore, the sequences of the claimed polypeptides and of the claimed polynucleotides are corresponding technical features which are common to all of Applicants' claims. These corresponding technical features serve to technically interrelate all of Applicants' claims. As such, Applicants' claims are linked to form a single general inventive concept, and Applicants are thus entitled to prosecute all of their pending claims in a single national stage application. Withdrawal of the restriction requirement is therefore respectfully requested.

In the event that the Patent Office does not apply the Unity of Invention standard to this national stage application, Applicants note that claims directed to methods of using the claimed polynucleotides for detecting polynucleotides by hybridization (i.e., claims 7 and 8), could and should be examined together with the product claims from which they depend, per the Commissioner's Notice in the Official Gazette of March 26, 1996, entitled "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)" which sets forth the rules, upon allowance of product claims, for rejoinder of process claims covering the same scope of products. Applicants presume these method claims will be rejoined, upon determining allowability of the product claims from which they depend.

It is also submitted that claim 1, drawn to the polypeptides of the invention, could be examined along with the polynucleotide claims without undue burden on the Examiner. A search for prior art to determine the novelty of the polynucleotides would substantially overlap with a search of the prior art to determine the novelty of the polypeptides encoded by the polynucleotides.

II. Restriction between individual polypeptide and polynucleotide sequences

In addition, Applicants traverse the requirement for election of a sequence as between elements in Markush groups (those elements being, respectively, SEQ ID NO:16-23 and SEQ ID NO:25-30, which encode polypeptides of SEQ ID NO:1-8 and SEQ ID NO:10-15, respectively, and SEQ ID NO:24). The Examiner's attention is directed to section D of M.P.E.P. section 1850, which recites the provisions of paragraph (f) of Part 1 (entitled "Instructions Concerning Unity of Invention") of Annex B (entitled "Unity of Invention") to the Administrative Instructions Under the PCT:

> **D. "Markush Practice"**
>
> The situation involving the so-called Markush practice wherein a single claim defines alternatives (chemical or non-chemical) is also governed by PCT Rule 13.2. In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in PCT Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.
>
> When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:
>
> (A) All alternatives have a common property or activity; and
>
> (B)(1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives; or
>
> (C)(2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.
>
> In paragraph (B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of the existing prior art. The structural element may be a single component or a combination of individual components linked together.

In paragraph (C)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved.

The fact that the alternatives of a Markush grouping can be differently classified shall not, taken alone, be considered to be justification for a finding of a lack of unity of invention.

When dealing with alternatives, if it can be shown that at least one Markush alternative is not novel over the prior art, the question of unity of invention shall be reconsidered by the examiner. Reconsideration does not necessarily imply that an objection of lack of unity shall be raised.

It is improper for the Office to refuse to examine that which applicants regard as their invention, unless the subject matter in a claim lacks unity of invention. The polynucleotides encoding the polypeptides of SEQ ID NO:1-8 and SEQ ID NO:10-15 (including the polynucleotides of SEQ ID NO:16-23 and SEQ ID NO:25-30), and polynucleotides of SEQ ID NO:24, are alternatives of a similar nature in that all of the claimed polynucleotide sequences encode oxidoreductase proteins. As such, the claimed polynucleotides share the common property/activity of encoding polypeptides which carry out oxidation/reduction reactions. In addition, the polynucleotides of the instant invention share a common structure in that they are all polynucleotide molecules. Furthermore, the claimed polynucleotides share a common utility in, for example, toxicology studies based on expression profiling.

Therefore, it is respectfully submitted that the requirement for restriction between individual polypeptide and polynucleotide sequences be withdrawn. In the event that the Patent Office refuses to withdraw this restriction requirement, then upon searching and examining SEQ ID NO:29, which encodes SEQ ID NO:14, and finding no prior art over which SEQ ID NO:29 can be rejected, the Examiner must extend the search of the Markush-type claim to include the non-elected species.

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

Respectfully submitted,

INCYTE CORPORATION

Date: June 16, 2003

Terence P. Lo, Ph.D.
Limited Recognition (37 C.F.R. § 10.9(b)) attached
Direct Dial Telephone: (650) 621-8581

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS

Claims 2, 6, 15, and 17-20 have been canceled, without prejudice or disclaimer.

Claims 1, 3-5, and 7-14 have been amended as follows:

1. (Once Amended) [A substantially purified] An isolated polypeptide [comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, and fragments thereof] encoded by a polynucleotide of claim 3.

3. (Once Amended) An isolated [and purified] polynucleotide encoding [the] a polypeptide selected from the group consisting of [claim 1] :

a) a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-8 and SEQ ID NO:10-15,

b) a polypeptide comprising a naturally occuring amino acid sequence at least 90% identical to an amino acid sequence selected from the group consisting of SEQ ID NO:1-8 and SEQ ID NO:10-15,

c) a fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-8 and SEQ ID NO:10-15, wherein the fragment has oxidoreductase activity, and

d) an immunogenic fragment of a polypeptide having an amino acid sequence selected from the group consisting of SEQ ID NO:1-8 and SEQ ID NO:10-15.

4. (Once Amended) An isolated [and purified polynucleotide variant having at least 70% polynucleotide sequence identity to the] polynucleotide of claim 3, encoding a polypeptide comprising an amino acid sequence selected from the group consisting of SEQ ID NO:1-8 and SEQ ID NO:10-15.

5. (Once Amended) An isolated [and purified] polynucleotide which hybridizes [under stringent conditions] to [the] a polynucleotide of claim [3] 23 at 30°C in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS.

7. (Once Amended) A method for detecting a target polynucleotide in a sample, the target polynucleotide having a sequence of a polynucleotide of claim 9, the method comprising [the steps of]:

(a) hybridizing the sample with a probe comprising at least 20 contiguous nucleotides comprising a sequence complementary to the target polynucleotide [of claim 6 to at least one nucleic acid] in [a] the sample, and which probe specifically hybridizes to the target polynucleotide, under conditions whereby [thereby forming] a hybridization complex is formed between the probe and the target polynucleotide or fragments thereof; and

(b) detecting the presence of the hybridization complex, wherein the presence of the hybridization complex correlates with the presence of the target polynucleotide in the sample.

8. (Once Amended) [The] A method of detecting a target polynucleotide in a sample, the target polynucleotide having a sequence of a polynucleotide of claim [7] 9, the method [further] comprising :

a) amplifying the target polynucleotide [prior to hybridization] or fragment thereof using polymerase chain reaction amplification, and

b) detecting the presence or absence of the amplified target polynucleotide or fragment thereof, and, optionally, if present, the amount thereof.

9. (Once Amended) An isolated [and purified] polynucleotide selected from the group consisting of:

a) a polynucleotide comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:16-30 [and fragments thereof],

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to a polynucleotide sequence selected from the group consisting of SEQ ID NO:16-30,

c) a polynucleotide complementary to a polynucleotide of a),

d) a polynucleotide complementary to a polynucleotide of b), and

e) an RNA equivalent of a)-d).

10. (Once Amended) An isolated [and purified] polynucleotide [variant having at least 70% polynucleotide sequence identity to the polynucleotide] of claim 9, comprising a polynucleotide sequence selected from the group consisting of SEQ ID NO:16-30.

11. (Once Amended) An isolated [and purified] polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:29,

b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:29,

c) a polynucleotide [having a sequence which is] complementary to the polynucleotide of [claim 9] a),

d) a polynucleotide complementary to the polynucleotide of b), and

e) an RNA equivalent of a)-d).

12. (Once Amended) [An expression vector] A recombinant polynucleotide comprising [at least a fragment of the] a promoter sequence operably linked to a polynucleotide of claim 3.

13. (Once Amended) A [host] cell [comprising the expression vector] transformed with a recombinant polynucleotide of claim 12.

14. (Once Amended) A method for producing a polypeptide encoded by a polynucleotide of claim 3, the method comprising [the steps of]:

a) culturing [the host] a cell [of claim 13] under conditions suitable for [the] expression of the polypeptide, wherein the cell is transformed with a recombinant polynucleotide, and the recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide of claim 3; and

b) recovering the polypeptide [from the host cell culture] so expressed.

New claims 21-27 have been added as follows:

21. (New) A method of screening a compound for effectiveness in altering expression of a target polynucleotide, wherein the target polynucleotide comprises a sequence of claim 10, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, under conditions suitable for the expression of the target polynucleotide,

b) detecting altered expression of the target polynucleotide, and

c) comparing the expression of the target polynucleotide in the presence of varying amounts of the compound and in the absence of the compound.

22. (New) A method of assessing toxicity of a test compound, the method comprising:

a) treating a biological sample containing nucleic acids with the test compound,

b) hybridizing the nucleic acids of the treated biological sample with a probe comprising at least 20 contiguous nucleotides of a polynucleotide of claim 9 under conditions whereby a specific hybridization complex is formed between the probe and a target polynucleotide in the biological sample,

the target polynucleotide comprising a polynucleotide sequence of a polynucleotide of claim 9 or fragment thereof,

c) quantifying the amount of hybridization complex, and

d) comparing the amount of hybridization complex in the treated biological sample with the amount of hybridization complex in an untreated biological sample, wherein a difference in the amount of hybridization complex in the treated biological sample indicates potential toxicity of the test compound.

23. (New) An isolated polynucleotide of claim 3, encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:14,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:14, wherein the polypeptide has pyrroline-5-carboxylate reductase activity,

c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:14, wherein the fragment has pyrroline-5-carboxylate reductase activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:14.

24. (New) An isolated polynucleotide of claim 3, encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:14, and

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:14, wherein the polypeptide has pyrroline-5-carboxylate reductase activity.

25. (New) An isolated polynucleotide of claim 3, encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:14.

26. (New) An isolated polynucleotide of claim 9, selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:29,

b) a polynucleotide a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:29,

c) a polynucleotide complementary to the polynucleotide of a),

d) a polynucleotide complementary to the polynucleotide of b), and

e) an RNA equivalent of a)-d).

27. (New) An isolated polynucleotide of claim 9, selected from the group consisting of:

a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:29,

b) a polynucleotide complementary to the polynucleotide of a), and

c) an RNA equivalent of a)-b).